DISORDERS OF THE BLOOD

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR CLAUDE E. FORKNER: To cover the treatment of the diseases of the blood in one and one half hours is a very large task. There are over 20 different varieties of anemia, several kinds of polycythemia, many hemorrhagic diseases, a dozen varieties of leukemia, plus the lymphoblastomas, myeloma, agranulocytosis and infectious mononucleosis.

Before we start the discussion, I wish to point out that any questions from the members of the panel during the course of any speaker's comments and any questions from the audience will be welcome.

Dr. Reznikoff, will you introduce the subject of the treatment of the anemias?

DR. PAUL REZNIKOFF: Mr. Chairman, Ladies and Gentlemen, the most important thing to remember about treating an anemia is to find its cause and eradicate it if possible. I can dismiss acute blood loss very

* Presented in the Monthly Panel Meeting Series, February 6, 1953, at The New York Academy of Medicine.

readily by saying that if one can keep the blood volume and blood pressure above a critical level the patient will recover, because we assume that the store houses in the body contain the raw materials necessary to produce blood. It is not so much a problem of anemia, but rather, the problem of shock. Whether it is advisable to give such an individual iron or other adjuvants is questionable.

The most important groups of anemias are those that are due to two main types of faulty bone marrow function. In the first place, one may have a normal bone marrow but it may not be receiving the raw materials necessary to produce hemoglobin and red blood cells adequately. The first of these materials that we think about is iron. It is essential to remember that administered iron is effective in iron deficiency anemia and in no other kind of anemia. How does one give iron? By and large and in most cases—and the exception I will mention later—iron should be given orally. Probably the most effective type of iron is ferrous rather than ferric, or reduced iron. It is more easily absorbed and less irritating. Probably the most effective way of giving iron by mouth is to start with relatively small doses, increasing the amount gradually. Iron usually is given after meals to avoid irritation. How much iron does one give? In general we can say that if an individual gets 300 mg. of iron as such, which would be about one gram of ferrous sulfate in divided doses, that individual is getting an adequate amount of iron. Most patients can be treated adequately with less.

MODERATOR FORKNER: *Dr. Reznikoff, how many tablets of ordinary ferrous sulfate would that be?*

DR. REZNIKOFF: Usually the patient can get along with two tablets three times a day.

MODERATOR FORKNER: *When does one employ intravenous iron?*

DR. REZNIKOFF: Rarely it occurs that a patient does not tolerate oral iron or is acutely anemic and there may not be enough time to wait for hemoglobin to develop properly, as in the instance of a woman about to deliver a baby. Moore has shown that if you give saccharated iron oxide up to about 100 mg. intravenously once a day you probably will not get into trouble. I say "probably" because he thinks it isn't desirable to continue to give iron intravenously over a long period of time.

Another important factor in the bone marrow is the maturation factor. It concerns such agents as vitamin B_{12}, liver extract and folic acid. Liver extract and B_{12} should be given intramuscularly in cases of

pernicious anemia. There are exceptions to that which I will mention presently. On the other hand, folic acid is given orally as in the treatment of sprue. How much liver extract or B_{12} should one give? We don't know exactly. In most patients with pernicious anemia *in relapse*, 15 to 30 micrograms of vitamin B_{12}, or 15 to 30 units of liver extract intramuscularly once a day until the reticulocyte count begins to fall. This usually is for about two weeks. These drugs may then be given three times a week, and then once a week. Thereafter one has to find out what the patient's maintenance dose may be. Some patients will get along quite well on 15 micrograms of B_{12} once a week. Others can get along with as little as 15 micrograms once a month. If a patient has neurological symptoms and signs it is important to give more rather than less. In most of those patients we give for maintenance, 30 micrograms of vitamin B_{12} or 30 units of liver extract once a week. How much folic acid should one give in sprue or in the megaloblastic anemia of pregnancy? My estimate would be anywhere from 15 to 30 or even 45 mg. a day in divided doses. That should be effective. There are other conditions in which folic acid might be given intravenously. I should mention that there is work going on at present indicating that combinations of vitamin B_{12} and folic acid by mouth may be effective. This is not accepted generally at present. We do not give folic acid to patients with pernicious anemia because we are sure that it will not prevent the occurrence or the progression of neurological symptoms and signs.

There are other substances which may be important in treating anemia brought about by faulty nutrition to the bone marrow. An example is thyroid substance in patients with hypothyroidism. In some patients with iron deficiency anemia perhaps you might give hydrochloric acid. Certainly most of the patients do not need it but we have had a few in whom the addition of hydrochloric acid has seemed to make quite a difference.

Shall one give copper or other heavy metals? There is no indication that human beings, certainly adults, need any of those because there is enough of those metals in the impurities of our food, water and medication, so that they need not be added.

Another type of bone marrow deficiency is a depressed bone marrow, the kind produced by x-ray therapy, benzol or the kind found in leukemia. This type of anemia we call refractory or aplastic. In such cases no drug will help the patient if one cannot get rid of the cause

and if the patient does not recover spontaneously. Transfusions may be used as a palliative remedy. I have seen no benefit from ACTH or cortisone in aplastic anemia.

Finally, in the defective bone marrow functions there is a group of conditions as exemplified by chronic lead poisoning, in which there seems to be a deficiency of hemoglobin formation from the porphyrins. Until the cause of the trouble is eliminated nothing helps the patient except transfusions.

There are many hemolytic anemias and in most of them one has to get rid of the cause of the trouble. I am talking about Streptococcus hemolyticus septicemia, malaria and so on. However, there are at least two types of hemolytic anemia in which something can be done for the patient quite aside from getting rid of the cause because in most of these cases we cannot get rid of the cause. I am talking about familial hemolytic jaundice, in which splenectomy is almost 100 per cent efficient, and the acquired hemolytic anemias in which splenectomy is not quite so efficient. Some physicians think splenectomy is not effective in the acquired hemolytic anemia, the kind characterized by a positive Coombs' test. Some of these patients do derive benefit from ACTH and cortisone. Most of the other types of anemia that are due to leukemia, Hodgkin's disease, neoplasm, sickle cell anemia, etc., are refractory to the medications mentioned. Transfusions may be used while one is treating the basic condition.

What about diet in the anemias? Well, of course, it is a good thing to have steak and roast beef, but that alone will not cure an iron deficiency anemia. You have to give the patients iron. I think an important factor in treating anemias is to realize that a transfusion does not cure an anemia. The anemia will have to be cured by removing the cause or in some other fashion. The bone marrow has to become effective. The transfusions are only palliative. They may be lifesaving but they are only palliative.

There are two other points I should like to emphasize before I leave the subject of anemia. One is that you should delay any treatment in anemia, except emergency therapy, until the cause is determined. That is essential. If you give a patient with pernicious anemia one injection of vitamin B_{12} and the next day take a bone marrow specimen for diagnosis, you will find that the bone marrow specimen may be entirely changed. Similarly if you give a patient iron and then after several weeks

try to determine what sort of an anemia it is, one finds that the pattern of the anemia has changed so that the diagnostician can no more make a diagnosis than a detective can determine the culprit if the fingerprints are wiped from some object. Again I emphasize, that it is important to find out the cause. A patient may have a carcinoma of the cecum and have an iron deficiency anemia. If iron is given he may feel much better but the result is that several months may elapse before one is able to operate upon the patient and perhaps save his life.

Finally in this question of anemia I should like to emphasize the fact that it usually is bad medicine to treat the patient with combinations of medications. If the patient is iron deficient he should get iron. If the patient has pernicious anemia, he should get liver extract or vitamin B_{12}. You don't combine these things. You give what is indicated.

MODERATOR FORKNER: Dr. Reznikoff, I would like to raise a point just there. *Do you know of any liver extracts that are now available that don't have B_{12} in them?*

DR. REZNIKOFF: As far as I can tell, no. They all have.

MODERATOR FORKNER: *So that our treatment now necessarily must be a combination of liver extract and B_{12} in the treatment of pernicious anemia. Isn't that true? Would any other members of the panel care to comment on that point? Is there no objection to the combination of liver extract and vitamin B_{12}? Would you say it is more advantageous to give B_{12} alone or the combination?*

DR. REZNIKOFF: I should say it is more advantageous to give it alone because it is less irritating and less expensive.

DR. JOSEPH H. BURCHENAL: There is one more point about iron and B_{12}. It is true one doesn't want to give them together generally but in a very anemic patient with pernicious anemia when the patient is building up his blood count, sometimes the stores of iron are low. I am sure you were going to mention that.

DR. REZNIKOFF: If a patient with pernicious anemia is iron deficient at any time during his treatment he should receive iron but not because he has pernicious anemia, but because he is iron deficient.

MODERATOR FORKNER: *How do you know he is iron deficient?*

DR. REZNIKOFF: By following the blood, seeing if the patient shows a relative decrease in hemoglobin and a marked decrease in hematocrit. Most patients don't require it.

MODERATOR FORKNER: You said nothing about the other vitamins.

DR. REZNIKOFF: The only other vitamin which I think is of significance is vitamin C because apparently it will convert folic acid into active citrovorum factor or folinic acid.

MODERATOR FORKNER: *Would you say it is good medicine or bad medicine to prescribe a lot of vitamins A, B, C and D and multiple vitamins in the treatment of the anemias?*

DR. REZNIKOFF: I am sure you know the answer but I will act as a good stooge. It is pretty bad medicine.

(Slide) If you look at this slide you will see an anemic rat represented and this rat has been weaned from an iron deficient mother and been on a low iron diet. You can see the red blood cell count goes down, the hemoglobin is down, the reticulocytes are within a certain zone. Nothing happened to it except continued anemia.

(Slide) If you look at the next slide you will see represented a litter mate who has received iron. The reticulocyte count goes up within seven days. The red blood cell count and hemoglobin follow suit. This is the biological curve of response to hematinics and the same kind of curve exists in the pernicious anemia patient who is receiving vitamin B_{12} or liver extract.

(Slide) Briefly I want to go into the question of polycythemia. There are many ways of treating polycythemia. I am going to restrict my remarks to polycythemia vera. In the first place there is irradiation. One can give spot irradiation over the spleen or bone marrow or one can give spray irradiation over the torso. Irradiation usually is given in the following way: 200 kilovoltage, one meter distance, 30 to 50 r, anterior and posterior every day, using a one mm. aluminum and one mm. copper filter for a total of anywhere from 100 to 250 r over each port. Radioactive phosphorus, P^{32} is being used extensively. It can be given either intravenously or by mouth. A typical illustration of how this works is as follows: You give 3.5 to 4 millicuries intravenously. After a few weeks, another dose of from one to three millicuries may be necessary. One patient I had, who was treated by Dr. Craver, weighed 80 kg., and he received six millicuries orally. Another effective method of treating polycythemia of course is to bleed the patients. Such blood I believe can be used for transfusion into anemic patients. Some physicians don't like to use it, but it is the best source of a high platelet containing blood that we have today. Dr. Dameshek of Boston likes to bleed his patients and give them diets low in iron. An effective method, although not used very

much, is one described by Dr. Forkner in 1933, in which he used Fowler's solution by mouth starting with 0.2 cc. increasing one minim, or 0.06 cc. a day, not a dose, until the patient gets up to 0.6 cc. three times a day after meals, or up to the point of tolerance which is characterized by anorexia.

Recently there has been some work showing that nitrogen mustard can be used effectively in polycythemia. My own results have not been as good as some others but it is effective. The dose is two-tenths of a mg. per kg. of body weight given intravenously in 50 cc. of saline on two successive days.

The final point I wish to make about polycythemia vera is true of all blood conditions. These patients are emotionally upset. You have to treat that. You have to give them a diet which will not irritate the gastrointestinal tract, avoiding roughage, spices and food which is too hot and of course there are complications which are many. Thromboses have to be treated, which is very difficult because you do not wish to keep them in bed. I wish to show you my last slide illustrating one case—

(Slide) This patient had a red blood cell count of about 11,000,000 per c. mm. and was treated so effectively with phlebotomies, x-ray therapy and acetylphenylhydrazine, that he became quite anemic. This was heroic treatment. He went for 56 weeks with a normal blood picture. When the red blood cell count began to go up again he was given more acetylphenylhydrazine, a tenth of a gram a day and went along for quite some time. Phenylhydrazine and acetylphenylhydrazine are hemolytic agents which formerly were used extensively in the treatment of erythremia. Later we gave him spray irradiation and he went along for 45 weeks again with a normal count. Treatment of this sort was continued for several years. He lived about ten years and died of pneumonia. That is about all I wish to say at this time Dr. Forkner.

MODERATOR FORKNER: Dr. Reznikoff, there are one or two points that I would like to raise here and the first is concerning polycythemia. I take it that you often use both a combination of phlebotomy and irradiation in the treatment to acquire a quick, good result.

DR. REZNIKOFF: We do.

MODERATOR FORKNER: The other point that I wanted to raise was about splenectomy in acquired hemolytic anemia. You said that many patients are not helped by splenectomy.

Dr. Rosenthal, would you comment on that? What is your experi-

ence with splenectomy in acquired hemolytic anemia?

DR. NATHAN ROSENTHAL: In the many cases that I have seen I believe that it is helpful in about one-third of the cases. In another third the patients improve but do not get entirely well and in another third the operation is absolutely useless and the patient sometimes goes on to a fatality. I believe that in acquired hemolytic anemia initial splenectomy may be of some value if the patient is in good condition. One should not wait until he gets in a poor state. With the aid of cortisone, patients do much better after splenectomy. Such treatment seems to slow the process a great deal but it is only of value in those cases in which the Coombs' test is positive.

MODERATOR FORKNER: *Are there any other comments from the panel on these points?*

DR. LLOYD F. CRAVER: How many acquired hemolytic anemias do you find have a positive Coombs' test?

DR. ROSENTHAL: In practically 90 per cent of the cases of acquired hemolytic anemia. In a patient who does not have a positive Coombs' test I think the prognosis is sometimes unfavorable.

DR. REZNIKOFF: Do you think, Dr. Rosenthal, that the hemolytic anemias found secondary to Hodgkin's disease, leukemia, and lymphoblastoma in general, have a positive Coombs' test?

DR. ROSENTHAL: They also have a positive Coombs' test and even in some of these cases splenectomy is indicated and occasionally a patient does do much better following operation than without the operation, but in other instances in which we have attempted splenectomy no good results were obtained.

DR. REZNIKOFF: Do you ever take out the spleen in polycythemia vera?

DR. ROSENTHAL: We never take out the spleen in polycythemia vera. Only recently I have seen one patient who was operated on for a tumor of the abdomen, the spleen was removed and after operation he proved to be a case of polycythemia vera. That is the second patient in my experience who has had a splenectomy but the diagnosis was not made preoperatively in this case. However, in another case in which the diagnosis was made the surgeon did perform splenectomy against our advice and this patient developed a tremendous thrombocytosis. The platelets increased rapidly to two million, three million, four million, one instance five million, and with the rise in platelets apparently, he bled

from all the mucous membranes possibly due to either thrombi in the venous channels, especially the capillaries or to defective clot formation and retraction. The gums especially were the site of hemorrhage. He kept on bleeding and transfusions could not keep pace with the severity of the hemorrhage.

MODERATOR FORKNER: Dr. Rosenthal, I think we will have to go on now. We may come back in the hour to some more comment and discussions. I would like you, Dr. Rosenthal, to take about 15 minutes to discuss the treatment of the hemorrhagic disorders.

DR. ROSENTHAL: We may summarize the subject by saying there are three types of hemorrhagic diseases: One due to changes either in the plasma thromboplastic factors, the blood platelets or other clotting factors; the second, due to vitamins or lack of vitamins, especially vitamin C and vitamin K, so-called idiopathic hypoprothrombinemias of various types and secondary hypoprothrombinemias. The third type is due to some form of toxicosis of capillaries, as in Schönlein's disease and in some cases of Osler's hereditary telangiectasia.

The two most important types of hemorrhagic diseases are hemophilia and the purpuras. These conditions are plasmatic in type. There is some deficiency in the plasma. Hemophilia, we used to think, was one disease, but recent work has shown that there are three protein clotting factors which when deficient can give the conventional clinical and clotting picture of hemophilia. In classical hemophilia, anti-hemophilic globulin is deficient. There is a deficiency in plasma thromboplastin component (PTC). Recently we have come across a third type, present in both males and females, caused by a deficiency in plasma thromboplastin antecedent (PTA) factors. These patients have deficiency of the thromboplastin and the treatment naturally would be the replacement of the deficient factor. We do know that these patients can have the thromboplastin replaced by fresh blood or by fresh-frozen plasma. At the present time the choice is fresh-frozen plasma which has all the necessary thromboplastin factor to improve the blood and bring it to normal within a short period so that hemorrhages of various types can be controlled promptly. It is especially to be noted that in children who develop open hemarthroses these can be prevented by prompt treatment with fresh-frozen plasma.

MODERATOR FORKNER: Where do you get the frozen plasma?

DR. ROSENTHAL: It is now available at the Blood Transfusion Asso-

ciation at West 102nd Street. It can be obtained by the hematologist or by the general practitioner for the use of hemophiliacs. I advise strongly that the treatment should be started at the first symptom, especially in children when blood begins to seep into the joints. In that manner one can control the hemarthroses.

MODERATOR FORKNER: *How often do you have to give the frozen plasma?*

DR. ROSENTHAL: Whenever an episode of bleeding occurs in the hemophiliacs of various types, either bleeding from gums, injury or hemarthrosis. In adults I would advise the use of two units of plasma whereas in children one unit is usually sufficient. It also applies to these other types of hemophilia I spoke about, because fresh-frozen plasma contains the thromboplastic factor which is deficient in their plasma. If fresh-frozen plasma is not available, naturally fresh blood transfusions should be given. I believe that bank blood has no effect at all in cases of anti-hemophilic globulin deficiency. PTC and PTA, however, are present in stored plasma, blood and serum.

MODERATOR FORKNER: *Dr. Rosenthal, in hemophiliac patients who bleed from the kidney have you found frozen plasma or transfusions are beneficial in stopping the bleeding?*

DR. ROSENTHAL: We find the best results can be obtained by fresh-frozen plasma. We can give a large amount of this. You can give two or three units whereas you would have to give twice as much blood in order to make it just as effective in the treatment and we recently have had patients with hemophilia with large blood exudation into the joints. They can be effectively treated with frozen plasma. Formerly, we used to rely to some extent on Fraction One prepared by the method of Cohn of the Harvard Medical School but this is not available and is sometimes subject to one drawback and that is the possibility of production of antibodies or anticoagulants in the patient's blood. This seems to occur rather rarely with frozen plasma.

The second main type of hemorrhagic disease is that of thrombocytopenic purpura. This is the most important of all because it is seen more commonly than hemophilia or any other forms of hemorrhagic disease. Here again we come to a disease which has different causes. At times it is idiopathic in type. Sometimes we can trace the cause to drugs, at other times to infection. In discussing this subject, I should like to review the last 100 cases of purpuric hemorrhage to see what we can actually

accomplish in thrombocytopenic purpura. First of all, the disease occurs frequently in children and usually runs a benign course.

(Slide) About 90 per cent of the children recover completely and only about 10 per cent are fatal cases or go on to a chronic state. You notice here that one of the most common causes of purpura in children is that following infections, or following contagious disease and occurs in the convalescent stage. These children always recover. The most severe form follows chickenpox and this is about the only group which may require transfusions.

(Slide) Secondly, we should be on the alert for acute toxic purpuras. They are not uncommon. We miss some of them because we do not question the patients adequately. I want to call attention to some of the recent ones we have had. Hair dye is an important factor in women. For that reason we see more purpura in these patients. We also have to be on the alert for quinidine. If we recognize this form of toxic purpura, the only treatment is stopping the offending drug. It is rarely necessary to transfuse such patients.

(Slide) There are other forms of acute thrombocytopenic purpura which are due to two other causes. One is megakaryophthisis in which there is complete absence of platelet formation in the bone marrow. Such patients do not do well with splenectomy or other treatments. This usually is an acute fatal disease. Second is so-called thrombotic purpura first described by Moschcowitz in which there is a marked diminution of platelets, severe bleeding but usually associated with some hemolytic anemia and also in most cases with azotemia. These patients usually run an acute fatal course and are not benefited by either transfusions or splenectomy.

(Slide) Then we come to the largest group of all, patients who have chronic thrombocytopenic purpura. They sometimes begin acutely and here again we have different causes for the purpura. One may be localized to bone marrow. The megakaryocytes are deficient in the formation of platelets; second, there may be a circulating antibody to platelets or change in the plasma of some type which affects the megakaryocytes and also possibly destroys platelets in the circulating blood, and third, there may be a type, which is not too common, in which the spleen is responsible by sequestration or thrombocytolysis of the platelets. For these three types the only curative treatment is splenectomy which is successful in about 80 per cent of the patients.

(Slide) In 20 per cent of patients with thrombocytopenic purpura we still have a considerable amount of trouble. The bleeding continues, because the disease affects only the megakaryocytes and is not due to outside influences such as circulating thrombocytolysins in the peripheral blood or due to some effect of the spleen on the megakaryocytes. These patients have lately been helped to a considerable extent by the use of cortisone which seems to affect the vascular system without altering the platelet level. Secondly, there may be some patients who have recurrences as the result of accessory spleens. These, however, are very few in number and should be checked by means of thorotrast. I should advise against the use of thorotrast if the patient shows Howell-Jolly bodies, or target cells in the blood. Their presence indicates that the splenectomy has been complete, and the cause is not in the spleen, but most likely in the bone marrow or elsewhere. Thirdly, there are some cases which cannot be controlled. We don't know the causes of these failures following splenectomy and in such instances we have to rely on periodic transfusions and cortisone.

The use of cortisone has become quite prevalent in thrombocytopenic purpura. I don't believe it should be used in children. In addition, it is valuable in preparing patients for splenectomy. In such cases it sometimes is helpful but in the majority of cases of thrombocytopenic purpura it does not serve the purpose. It does not change the bone marrow and it does not increase the platelets and the bleeding may continue so that one may be using something which is not very effective and may delay splenectomy, which may be curative.

(Slide) The first slide showed the megakaryocytes after splenectomy, the tremendous numbers of the platelets. It should have been shown last.

(Slide) This is the bone marrow in a case of thrombocytopenic purpura showing a tremendous increase in megakaryocytes, with unusual vacuolization. In most cases of thrombocytopenia only about 6 per cent of the megakaryocytes show platelet formation whereas normally over 20 per cent do.

(Slide) Here is another typical instance of this condition with the vacuolization of the cytoplasm. Here is a patient who developed a recurrence following operation.

(Slide) The patient had done very well for over a year and then had a recurrence and was treated with cortisone by mouth with an excellent

result. The cortisone was stopped and you notice the recurrence again and then cortisone was started again, 100 mg. daily, and another remission set in. At the present time this patient is being treated with about 25 mg. of cortisone daily and the platelets have become normal.

(Slide) Another overlooked treatment of purpura is that of snake venom. It has fallen into disuse but I think in many instances it has helped. Recently a patient was splenectomized because snake venom, which had controlled the purpura, was no longer available. In another instance, in which the patient had very few megakaryocytes in the marrow, the purpura was well controlled by snake venom. However, the patient or his doctor insisted on having a splenectomy, which was done. The patient showed no good effects from the splenectomy and was treated unsuccessfully with cortisone. Snake venom was resumed and controlled the bleeding. So we must consider the use of snake venom as one of the treatments for thrombocytopenic purpura. I don't know whether I have time to discuss other forms of purpura. Have I any more time left?

MODERATOR FORKNER: I think we had better leave that for the end.

There are one or two points. I would like to ask, what about local bleeding in such disorders as leukemia, for example, or thrombocytopenic purpura, local bleeding from the nose and from the gums? Is there any agent that may be used?

DR. ROSENTHAL: Local bleeding from the gums and nose is difficult to control in purpura or in leukemia due to the thrombocytopenia. Frequently we use Gelfoam and Oxycel but they usually do not work too well. The only treatment in these cases is a "fresh blood" transfusion, if the patient has lost sufficient blood.

MODERATOR FORKNER: *Dr. Rosenthal, you mentioned fresh blood transfusion. Why not banked blood?*

DR. ROSENTHAL: Banked blood on standing loses the effect of the blood platelets. The blood platelets deteriorate rapidly, within 24 hours following removal of the blood from the body; and in fact some believe that collecting blood in ordinary citrate causes a marked defect in the platelets. We have shown a long time ago that citrate injures platelets. For that reason we have the paradoxical reaction, that is, in the test tube the citrate prevents coagulation but if you inject large amounts of citrate in the circulating blood it increases the coagulability of the blood due to its effect on the platelets.

MODERATOR FORKNER: *What about hemophilia, is it necesssary to use fresh blood or may one use banked blood?*

DR. ROSENTHAL: One must always use fresh blood in classical hemophilia or anti-hemophilic globulin deficiency. Banked blood is ineffective; only plasma which has been frozen immediately after blood collection contains adequate amounts of the anti-hemophilic globulin.

MODERATOR FORKNER: *Will you say, Dr. Rosenthal, that in any blood dyscrasia in which bleeding is a manifestation, it is preferable to use fresh blood than banked blood?*

DR. ROSENTHAL: That is my belief, yes.

MODERATOR FORKNER: *The other members of the panel, do they agree with that?*

DR. CRAVER: Yes.

MODERATOR FORKNER: I think that is one of the common errors that is made. You can replace blood loss with bank blood. To stop the bleeding one must use fresh blood.

I believe we have to go ahead now. *Dr. Burchenal, will you tell us something about the treatment of acute and chronic leukemia?*

DR. BURCHENAL: In contrast to the subjects that the two previous discussers have been handling, leukemia is a disease for which at the present time there is no cure. That, however, does not mean that therapy is not indicated because considerable can be accomplished by treatment in this disease. In some cases life can be prolonged somewhat. In other cases the effective useful life of the patient can definitely be prolonged, although the actual survival time may not be. For these reasons we think that the treatment of leukemia is important.

First, Dr. Forkner has asked me to mention two diseases which are sometimes confused with leukemia but are not the same disease. For these two diseases, infectious lymphocytosis, first described by Smith and his group, and infectious mononucleosis, there is no particular treatment at the moment. They are benign diseases. The important thing is to distinguish them from leukemia. Infectious mononucleosis has been treated by Aureomycin but the consensus now seems to be that probably there isn't too great benefit from treatment with this drug. At any rate both of these are self-limited diseases which cure themselves.

As to the leukemias, I would like to divide them into the chronic myelocytic, the chronic lymphocytic and the acute leukemias. There are many other subdivisions of these but I believe that this will suffice.

In chronic myelocytic leukemia treatment can accomplish a good deal; although the actual survival time of the patient is probably not increased, his actual useful life is usually prolonged to within a month or so of the time of his death, so that he is kept much more comfortable and a much more useful member of society. The treatment of choice in most cases of chronic myelocytic leukemia, if all the facilities are available, is deep x-ray therapy over the spleen, given in small doses in the new case, say 50 r daily for three days, wait a week, see whether more therapy is necessary, and usually it will be, until the white blood cell count is brought down to the level of about 30,000 per c. mm. Usually after therapy is stopped the count will coast down even lower. Excellent remissions can be brought about by this form of treatment. Others prefer using spray x-ray therapy where the total body is irradiated or the body is divided into two large ports, one from the waist to the top of the head and the other from the waist down to the soles of the feet. By giving small doses, perhaps 10 to 20 r the first week and then gradually giving more and more radiation as indicated, the patient may be brought into remission. Osgood in particular feels that the patient's count should be kept below 30,000. At any time it rises above 30,000 further therapy should be given. This disease can also be treated by total body irradiation by means of radiophosphorus. This has some localizing effect in the bone marrow and in the lymphoid tissues so that the effect is a little more specific perhaps to the leukemic tissue than it would be with total body irradiation but even then it is much like total body irradiation. The usual dose is a tenth of a millicurie per kilogram, so that the average 150 pound patient would get a dose of about 7 millicuries. That dose usually will suffice to bring the count down reasonably well and hold it down for a considerable period of time. It should not be repeated within six weeks as a general rule. With all types of therapy, x-ray therapy and chemotherapy as well, patients differ tremendously so that these dosages that I am giving are by no means hard and fast dosages.

In addition to radiation therapy, chemotherapy can be used in the treatment of chronic myelocytic leukemia. Arsenic has been used with excellent results in the form of Fowler's solution, starting with a rather low dose and increasing to the patient's tolerance. Urethane can also be used, and if the patient will tolerate it well, does not have too much nausea and vomiting, and does not get too drowsy, urethane is an excellent method of keeping the patient in remission for a long period

of time. Nitrogen mustard, HN_2, can also be used. There, however, the treatment has to be given intravenously and it is my feeling that nitrogen mustard by being given over a short period of time, say a course of a tenth of a milligram per kilo daily for four doses, does not give you quite the smooth control that some of the other forms of therapy give.

(Slide) This is the nitrogen mustard. It shows the typical toxic effects that you may get, the nausea and vomiting, from a single course, the depression of the bone marrow if too much is given. This has one advantage over urethane in that although it causes nausea and vomiting, the course is given over a short period of time and then the patient ceases to have his nausea and vomiting. On the other hand, there is another compound, which is perhaps more satisfactory.

(Slide) It is TEM or triethylene melamine, which you can see is fairly closely related to the nitrogen mustard transformation product. This compound, triethylene melamine, can be given by mouth and in addition it does not cause nausea and vomiting. It can be given to the patient on an outpatient basis and small maintenance doses can be given. In that way the patient is kept in a smooth remission. We have found this fairly satisfactory in maintaining patients with chronic myelocytic leukemia in remission. There are other compounds which are being tried, antimetabolites, which may or may not have an effect on this disease. It would appear for the present time the x-ray and these chemotherapeutic agents of which I have spoken to you are the best methods of therapy. All of these will work in the patient with chronic myelocytic leukemia in the early stages and up until the time that he reaches the terminal acute stage, as shown usually by an increase in fever, increase in the percentage of blast cells and promyelocytes in the marrow and peripheral blood, oftentimes a fall in platelets, and sometimes an increase in the size of the peripheral lymph nodes. When he reaches the acute stage, however, there is very little therapy that will work. X-ray, at this stage, has no beneficial effect nor usually do the other chemotherapeutic agents. Amethopterin has been tried without success. Although it is frequently effective in acute leukemias in children, it does not influence the course in chronic myelocytic leukemia. We desperately need a compound which will do just that.

In chronic lymphocytic leukemia, characterized by large lymph nodes, often by enlargement of the liver and spleen and occasionally subcutaneous masses, localized x-ray therapy to the nodes probably is

the treatment of choice. Spray x-ray also can be used. P^{32} is quite satisfactory in types of chronic lymphocytic leukemia in which the count is high, but in which the patient otherwise does not have very large masses.

Chemotherapy can be given with triethylene melamine but here one should be very cautious in the dose that is given. Rather than giving 5 mg. daily for two to four days, one must give the smaller dose 2.5 mg. a day for perhaps two days and watch the patient very closely. Good results can be obtained with this compound only if the patient is watched very cautiously because patients are usually very sensitive to this drug. Steroids can be used in the treatment of chronic lymphocytic leukemia, particularly those cases in which there is acquired hemolytic anemia as well.

MODERATOR FORKNER: *By steroids you mean cortisone and ACTH?*

DR. BURCHENAL: Cortisone and ACTH and compound F as well. Sometimes they do not cause a characteristic fall in the white count. Usually the white count rises at first but the liver and spleen will decrease in size as well as the node masses.

(Slide) Now let us go on rapidly to the acute leukemias. There are various types of acute leukemia. In certain types in children with acute leukemia we think that survival time definitely can be prolonged by therapy, in a few cases, but not by any means in all. Children, with this disease as a general rule, respond much better than young adults and adults over the age of 30 rarely respond well, in my experience, to almost any form of therapy. There are two methods of therapy that we have at the present time, the antimetabolites and the steroid hormones, such as cortisone and ACTH. There are several antimetabolites which are being used experimentally at the present time. The only ones that have any practical use at the moment are the folic acid antagonists, particularly Aminopterin and Amethopterin.

(Slide) The formula of folic acid is at the top. In the four position there is a hydroxyl group. By altering that slightly chemically, as in the second formula, one has an amino group in the four position, and a very potent folic acid antagonist. This compound apparently goes in the enzyme systems into which folic acid ordinarily enters but once in there it cannot be utilized. It blocks the system and creates a relative deficiency of folic acid. The result is that the whole body has a relative deficiency of folic acid, but since apparently some types of leukemic cells need folic acid, or its biological products, more than do the normal cells, these

leukemic cells are specifically damaged by the antimetabolite therapy.

MODERATOR FORKNER: *Dr. Burchenal, is folic acid in ordinary vitamin B complex preparations that are so highly advertised?*

DR. BURCHENAL: Unfortunately it is getting to be more and more. In acute cases it is better to stay away from folic acid and citrovorum factor.

MODERATOR FORKNER: And stay away from the vitamin B complex.

DR. BURCHENAL: I would not feel so strongly about B_{12}. They seem to be tucking folic acid into other preparations.

MODERATOR FORKNER: *So it would be wrong to give patients with leukemia and some of the other disorders vitamin B complex?*

DR. BURCHENAL: I would think so.

DR. CRAVER: Do you feel there is any evidence that folic acid makes leukemia worse?

DR. BURCHENAL: We think so. Dr. Farber noted in patients treated with something like folic acid that the lesions looked much more severe, as though the lesions were moving on much more rapidly. In our study we felt the citrovorum factor, which is a counterpart of folic acid, definitely seemed to make a few patients worse.

MODERATOR FORKNER: *I would like to interject one point here. It is my own feeling that doctors generally and the public generally are consuming much too much in the way of vitamins and that very often these might be harmful. Would any member of the panel take issue with that statement?*

DR. BURCHENAL: I would certainly agree with that.

DR. REZNIKOFF: Which way are they harmful, except the expense?

MODERATOR FORKNER: We just heard of one instance.

DR. REZNIKOFF: The normal individual?

MODERATOR FORKNER: We just heard this instance in which it is possible that the folic acid brings about a worsening of the leukemic state. I think it is also possible that it may have other effects, possibly lighting up a latent leukemic state in an individual who might not develop it so soon. Of course, we know that vitamin D in large doses is harmful. There is other evidence to suggest that other vitamins in excess are harmful.

DR. BURCHENAL: The usual dose of Amethopterin for a child is 2.5 mg. a day given by mouth. After a period of three to six weeks one may expect to see, in say 30 to 50 per cent of the children, remissions. A mar-

row looking like this (indicating) originally with a single cell picture will then change—

(Slide) to one in which there are myelocytes, megakaryocytes, some of the more normal erythrocyte elements and polymorphonuclears. The marrow will return to normal function, produce its own hemoglobin and its own platelets.

(Slide) There are also a certain number of toxic lesions from the folic acid antagonists. You see here an ulcer of the lip caused by therapy. Here are ulcers on the uvula and on the pharynx.

(Slide) And here are some ulcers on the hard palate. These are tender and painful and the patients usually will tell you about them. They are not in themselves dangerous but they are an indication of what may be going on further down in the gastrointestinal tract, and therefore it is important to stop therapy once these are noted.

(Slide) This shows the sort of improvement one can get with treatment with folic acid antagonists, Amethopterin. The top line shows the marrows, the black shows the percentage of leukemic cells in the marrow. You can see improvement in marrow each time treatment was given. About six courses of treatment were given over a period of a year and one-half. The patient responded each time. Now that is an exceptional case. Usually patients develop resistance more rapidly than this.

(Slide) And eventually the leukemia will become completely resistant to therapy. ACTH and cortisone are also useful in the treatment of the acute leukemias in children and in young adults. You can see the dosage there, ACTH usually 25 mg. four times daily, cortisone 100 to 400 mg. daily, depending upon the size of the patient.

(Slide) This will cause typical remissions in acute leukemias. You can see here that the stem cells in the marrow sometimes disappear very rapidly. The erythropoietic elements come back, the eosinophils fall and the reticulocytes rise generally. The remissions are generally short-lived. In children they can be repeated once, sometimes twice, in our experience rarely more. In young adults we have not seen them repeated at all, with the possible exception of one case.

(Slide) Here is a good example of a young doctor in whom an excellent remission was obtained at first and a rapid development of resistance so that when the disease relapsed treatment at the same dose as noted on the top of the slide, or at double, or quadruple, the dose had no effect on his disease. His white count remained high and he died despite therapy.

(Slide) This slide shows that a patient exhibited an excellent response to Amethopterin, but later the same dose of Amethopterin caused no improvement in the marrow. At that time cortisone was still able to produce a remission. This demonstrates that although a patient is resistant to Amethopterin he still may respond to cortisone or ACTH and vice versa.

That brings us then to one final thing. How do we decide what drug to use in acute leukemia? We prefer Amethopterin if the patient can tolerate it. So, if the patient is a child under the age of 10 with a white count under 50,000 and looks as though she would live for three weeks without therapy, we give Amethopterin by preference. If the patient, on the other hand, is a young adult or a child with a white count over 50,000 or a child who is obviously very sick, we start with cortisone and then return to Amethopterin at a later date. What are the results of therapy? If we compare 150 cases treated at Memorial Hospital before the days of the folic acid antagonists, two were surviving at the end of a year, after the first symptoms of leukemia. Of the patients treated with Amethopterin and with cortisone and with ACTH, 40 out of 154 were alive at the end of a year, 13 at 18 months, 7 at two years. After two years the survivals rapidly dropped off. There seems to be some increase in survival time in patients with acute leukemia treated by this method. The idea of course is to keep them going in the hope that something new may be discovered which may be of greater benefit.

MODERATOR FORKNER: Thank you, Dr. Burchenal.

Dr. Craver, will you discuss the treatment of the lymphomas?

DR. CRAVER: I shall have to skip very lightly over many aspects and omit some altogether because of the brief time available.

By the malignant lymphomas we mean such conditions as Hodgkin's disease, lymphosarcoma of the various types such as giant follicular lymphosarcoma, lymphocytic lymphosarcoma, reticulum cell lymphosarcoma or reticulum cell sarcoma and mycosis fungoides or granuloma fungoides. Statistics from the New York City Health Department a few years ago showed that of all the deaths from cancer, about 16 per cent were due to the malignant lymphomas and the leukemias. To a large extent they affect persons in their youth or in their prime of life. Another point is that, in general, they are very susceptible to constitutional therapeutic agents of various kinds. To a very large extent these diseases, the leukemias and malignant lymphomas, have become the prime test

objects for trials of newer constitutional methods for the treatment of cancer.

One point I would like to make is that the early biopsy in a case of Hodgkin's disease or lymphosarcoma may be quite unreliable. Even though the first biopsy turns out to be reported as chronic lymphadenitis or hyperplastic node, or something of that sort, if the clinical indications are there, the suspicion should be maintained and as soon as feasible another representative node or bit of tissue, wherever it may be, should be obtained.

I would like to point out also that the prognostic significance of the subdivisions of Hodgkin's disease into paragranuloma, granuloma and sarcoma are by no means as rigid as such divisions suggest. We have seen patients with the typical course of Hodgkin's disease, more aggressive even than average, and yet peripheral lymph node biopsies have suggested the structure of paragranuloma. On the other hand, by no means does every patient with a biopsy of Hodgkin's sarcoma have a certainty of being dead within two or three years. Such a patient may live as long as 10 or 15 years.

Certain modes of onset that can throw one off the track in diagnosis might be mentioned. For example, a whole series of cases could be collected of Hodgkin's disease of the mediastinum in which the disease has caused a fullness in the thyroid region or the disease has actually grown into the thyroid region, or actually into the thyroid, so that the first thought in regard to diagnosis has been that of goiter.

Another less common type simulates a mediastinal tumor or cardiac anomaly, particularly with flattening of the left border of the heart or an apparent enlargement of the pulmonary conus. We have one such patient now who had a node in his groin that was assumed to be due to epidermophytosis. It was watched for three and one-half years. The peculiar shape of his heart was watched for a year until finally when he was not feeling so well it was found that the mediastinal shadow had widened. Then, for the first time, the node in the left groin was removed and found to be Hodgkin's disease. It is well to remember that a lump in a woman's breast may not be fibroadenoma, may not be a cyst. It may not be carcinoma of the breast. It may be the first manifestation of lymphosarcoma. The onset of reticulum cell sarcoma, apparently primary in bone, is now a well known condition. It requires prompt radiographic diagnosis, which at times may be rather difficult to make and usually

requires a biopsy for definitive diagnosis.

Another mode of onset is the appearance of a little button of reddish purple color in the skin somewhere, most often in the scalp. Especially in young adults this may be the first manifestation of a lymphosarcoma or reticulum cell sarcoma.

Another mode of onset is the appearance of a growth in the periorbital region, in the subconjunctival region, or in the lids, a lymphoma that on biopsy may be regarded by the pathologist as benign, so-called benign lymphoma, but which may be the heralding sign of a process that is going to become generalized within a year or two. With the fact that these malignant lymphomas can involve any tissue whatsoever in the body, it is easy to understand that not only may the early diagnosis be difficult but also that the patient presents an ever recurring diagnostic problem. With the various system and tissue involvements that he may have in the central nervous system, the lungs, the heart, the gastrointestinal tract, the kidneys and so on, the problem of diagnosis keeps recurring.

The treatment of the malignant lymphomas has to be very much individualized. In general the idea, the philosophy is rather simple. The details may be most complex. The simple idea of the philosophy is to sort the cases out as to whether they are presenting a strictly localized process on the one hand, or whether at the other extreme they are presenting a uniformly or widely disseminated process. If the process is localized then local aggressive treatment is indicated, whether that be by radical irradiation or perhaps even radical surgery, followed by irradiation. In Hodgkin's disease and lymphosarcoma, I believe that applies mostly to upper cervical nodes. If the nodes are largely at the base of the neck, even though you find nothing else, you always suspect that there may be something in the torso down below in the thoracic or abdominal region and that this mass of nodes at the base of the neck is merely a signal of something that has been going on before. If the case is one of wide generalization, then the treatment becomes very much, as in chronic leukemia, a matter of palliation, which may be in the form of local radiation, judiciously employed. In some cases even wider radiation, as with spray or total body irradiation may be indicated. Also of course constitutional agents such as nitrogen mustard and the analogue, triethylene melamine, or TEM may be used.

There exists also the intermediate group of cases in which the disease

was strictly localized at first but has begun to spread but has not spread universally. The disease is still confined to a regional distribution relatively, such as in the mediastinal and supraclavicular nodes. In such instances it is a matter of individual choice whether treatment shall be by radiation alone or whether you shall precede it by nitrogen mustard or give nitrogen mustard concomitantly with the radiation. A whole hour could be spent on the treatment of malignant lymphomas complicated by pregnancy in women but we cannot take time to go into that today.

MODERATOR FORKNER: We cannot go into further details on these subjects but we have a series of questions here which I will present to the various members of the panel and I will ask them to make telegraphic answers. *Here is a question: Does the intravenous application of iron produce hemosiderosis?*

DR. REZNIKOFF: Apparently it does, but I know of no reported case. Transfusions, if given over a great period of time, as practiced in cases of aplastic anemia may result in hemosiderosis.

MODERATOR FORKNER: *Another question is submitted in writing. What is the percentage of Rh-negatives in the colored population and does it increase as the skin becomes lighter?* This is not a question of treatment but perhaps someone would care to answer. Dr. Rosenthal.

DR. ROSENTHAL: It is about one or two per cent in Negroes, and there is some increase in mulattoes as shown in various reports in the West Indies. It is very uncommon in Chinese, probably less than one per cent Rh-negative.

MODERATOR FORKNER: *Another question: Does one get serum hepatitis from frozen plasma?*

DR. ROSENTHAL: The plasma can transmit hepatitis, but so far we have been fortunate. In all the patients that I have seen we have not observed homologous serum jaundice but it is to be expected.

MODERATOR FORKNER: *Here is a question: Is liver extract of any use in disorders other than pernicious anemia?*

DR. REZNIKOFF: It may have some use in sprue although folic acid is better. Its value as a so-called general tonic is, I think, to put it politely, greatly exaggerated.

MODERATOR FORKNER: *Do you believe that liver extract should be used as a treatment for any disorder other than certain of these macrocytic anemias, Dr. Reznikoff? Is there any evidence to indicate it is of any value?*

DR. REZNIKOFF: I don't think so.

MODERATOR FORKNER: *I find that patients routinely are receiving B_{12} from almost all physicians for some reason or other. Is this B_{12} of any value in any condition other than the macrocytic anemias?*

DR. REZNIKOFF: I don't think so.

MODERATOR FORKNER: *Does any other member of the panel take issue with that?*

DR. ROSENTHAL: I agree it has no influence except in pernicious anemia and sprue.

DR. REZNIKOFF: Similarly, iron has no use except in iron deficiency anemia.

MODERATOR FORKNER: *Do the hematologic complications following the use of chloramphenicol or Chloromycetin mean that these drugs should not be used?*

DR. ROSENTHAL: I would stop using chloramphenicol. It causes aplastic anemia, usually an irreversible type. If only a small amount is taken the patient may recover, but otherwise the aplastic anemia is fatal.

DR. REZNIKOFF: I should like to modify or disagree to this extent, that there is no drug we have today that is so effective in typhoid fever as chloramphenicol and I think that is the only condition in which it should be used. As a rule its use is over a short period of time, usually not more than three weeks. I do not think it ought to be used as a long continued agent in such conditions as urinary tract infections.

DR. BURCHENAL: We have seen a fair number of infections with Staphylococcus aureus hemolyticus in which the organism was resistant to Terramycin, Aureomycin and penicillin but sensitive to Chloromycetin. I think in a desperately ill patient that should be an indication, but there should be a real and urgent indication for its use.

MODERATOR FORKNER: One must balance the hazards.

DR. ROSENTHAL: I agree with such exceptions.

MODERATOR FORKNER: *Another question: Are there other antibiotics such as Aureomycin, Terramycin, penicillin or the newer antibiotics which cause blood dyscrasias?*

DR. ROSENTHAL: No, I do not think so.

MODERATOR FORKNER: *What treatment, excluding transfusions, would you suggest for the blood disorder called agnogenic myeloid metaplasia or myelofibrosis? Is liver, or B_{12} or folic acid indicated? Dr. Reznikoff, we will let you answer that.*

DR. REZNIKOFF: There is no other treatment.

MODERATOR FORKNER: *Does everyone agree?*

DR. ROSENTHAL: I agree.

DR. BURCHENAL: Except possibly *not* doing a splenectomy.

MODERATOR FORKNER: *What is the value of platelet transfusions in thrombocytopenic purpura, Dr. Rosenthal?*

DR. ROSENTHAL: I don't believe it is of any value because the patient becomes resistant to the transfusion of platelets and develops more antibodies for the destruction of platelets. The same occurs in aplastic anemia. When you give the first platelet transfusion in aplastic anemia the platelets may remain in the blood for about four days. These platelets remain in the blood only a short time in thrombocytopurpura. I have seen platelets transfused from about ten donors. After the transfusion we have seen very few platelets although the bleeding may be controlled for a short time. Platelet transfusions seem to be of most value as an emergency measure to check an acute severe bleeding episode in a patient with thrombocytopenia.

MODERATOR FORKNER: *Dr. Rosenthal, what is the treatment for Henoch's purpura?*

DR. ROSENTHAL: There is no treatment. It is a self-limited disorder. Occasionally we use the steroids in some cases with only fair results.

DR. REZNIKOFF: Dr. Rosenthal do you think platelet transfusions might be indicated in preparation for splenectomy in patients with thrombocytopenic purpura?

DR. ROSENTHAL: Occasionally that has been done with good results. However, it is usually not necessary.

MODERATOR FORKNER: *Dr. Craver, I am going to ask you this one: What are the morphological differences in the blood and bone marrow, between acute and chronic leukemia?*

DR. CRAVER: A matter of degree to some extent because there may be certain borderline cases in which the hematologist can only suspect that this is perhaps a chronic leukemia verging toward an acute stage, but in cases of well marked chronic myeloid leukemia versus acute myeloid leukemia, the distinction is quite marked in the marrow. In acute leukemia you would have a high number of blasts and have immature cells and relatively few of the more nearly mature cells such as would be seen in the marrow of the normal individual or in the marrow of the patient with chronic myeloid leukemia.

MODERATOR FORKNER: *Is there any indication, Dr. Burchenal, that B_{12} reacts in any way as does folic acid in making leukemia worse?*

DR. BURCHENAL: Not as far as we know, no, sir.

MODERATOR FORKNER: *Are there any other questions from the floor? We can take one or two more minutes concerning the leukemias and lymphomas.*

DOCTOR: What do you think of Custer's classification of grouping all lymphomas under one heading?

MODERATOR FORKNER: Dr. Craver.

DR. CRAVER: You mean the diagram he has published?

SAME DOCTOR: Yes.

DR. CRAVER: I think it is well to have such diagrams. He has attempted to show in a schematic form his concept of the relationships.

DOCTOR: Does one treat a chronic leukemia or Hodgkin's disease in a patient who presents no symptoms?

DR. CRAVER: I would like to take that one. I am utterly opposed to withholding treatment for an early localized Hodgkin's disease, a principle which is practiced even in some university tumor clinics. I think that the treatment for the patient with early Hodgkin's disease, if you can be convinced that it is an early, localized process, should be directed toward trying to wipe that disease out. By doing so we have a chance for long remissions of say 18-20 years. I think the proposition is quite different in the case of leukemia, which is a generalized disease by the time anybody can diagnose it. Therefore, in leukemia, your treatment must be only that which will improve the patient. If he is symptom-free, what have you to improve?

MODERATOR FORKNER: I want to take this opportunity of thanking the members of the panel for coming here and for giving to us their expert views in this complicated and controversial field.